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RATIONALE BEHIND THE COMBINATION OF SULFONYLUREA AND METFORMIN IN DIABETES MELLITUS

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ABSTRACT

The prevalence of diabetes in India has been growing by leaps and bounds. The statistics in this regard are quite alarming. It is obvious that in a country like India, the rising prevalence of diabetes with its complications is likely to produce severe constraints on health care budgets in future. This explosion of diabetes in India has been viewed with serious concern by the WHO and the International Diabetes Federation (IDF). The two principal defects in type 2 diabetes are insulin deficiency and insulin resistance. Therefore, combining an insulin-providing agent with an insulin sensitizing agent will augment the efficacy of current anti-hyperglycaemic agents. This is the rational for the development and marketing of sulfonylurea/metformin combination tablets. The ultimate or primary goal of therapy for type 2 diabetes is to prevent the mortality and morbidity related to the microvascular and macrovascular complications. Since these disorders are life long, reduction in the number of tablets and daily doses is a very important consideration from the patient point of view. It is increasingly obvious that to achieve this on a global perspective will have to identify better and more effective treatment strategies to maintain tight glycaemic control.

INTRODUCTION: More than 33 million people know they have diabetes; and the number is climbing steeply. India has the dubious distinction of having the largest number of people with diabetes. The picture of diabetes in India is considerably different from that seen in the west. Managing diabetes has to be tailored to our Indian needs.

Type 2 diabetes mellitus emerges as a result of multiple pathophysiologic changes. If the pharmacotherapy of type 2 diabetes should be tailored to the underlying pathophysiology, it would be necessary to use a combination of agents with complementary mechanisms of action. The two principal defects in type 2 diabetes are insulin deficiency and insulin resistance. There is much evidence to suggest that initiating therapy with lower doses of two agents that have complementary effects can increase the overall efficacy and decreases the incidence of adverse effects. It is increasingly obvious that to achieve this on a global perspective we will need to identify better and more effective treatment strategies to maintain tight glycaemic control. Although patient compliance is one of the most important aspects of the management of diabetes mellitus, low rates of compliance have been documented. Patients receiving combination treatment (2 tablets) who are switched to fixed dose combination therapy exhibited significantly greater compliance after the switch.

The UKPDS (United Kingdom Prospective Diabetes Study) confirmed what was already evident to most physicians in type 2 diabetes i.e. eventually most patients will not be able to maintain glycemic control with a single agent. Diabetes is a chronic progressive disorder. The progression of diabetes results from a vicious cycle of insulin resistance and β-cell failure. Excess circulating glucose in turn itself is damaging to the β-cell (Commonly referred to as glucotoxicity) and may further accelerate the progression of the disease. Thus, loss of β-cell function is inevitable in patients with diabetes regardless of the treatment modality. The UKPDS indicated that by 6 years after the diagnosis of diabetes more than half of the patients needed more than one pharmacological agent to maintain glycemic control [1-5].

RATIONALE BEHIND THE COMBINATION OF A SULFONYL- UREA AND METFORMIN: Sulfonylurea and metformin have different mechanisms of action. Sulfonylurea mainly decrease blood glucose levels by stimulating insulin release from the pancreatic β-cells whereas metformin reduces blood glucose levels predominantly by improving hepatic and peripheral tissue sensitivity to insulin i.e. decreases hepatic and peripheral insulin resistance by decreasing affinity of insulin receptors towards insulin and by increasing the number of insulin receptors.

Thus, decreases hyperinsulinemia. It also decreases hepatic gluconeogenesis thereby decreasing high glucose output, reduces intestinal absorption of glucose and reduces blood glucose levels (fasting and post-prandial). Decreases weight thereby improves insulin resistance. Metformin also has beneficial effects on serum lipid levels and fibrinolytic activity, thereby decreasing the cardiovascular risk. Because of their complementary mechanisms of action, combination therapy with sulfonylurea and

metformin is rational and is associated with additive beneficial effect on the glycemic control. Combination therapy with a sulfonylurea and metformin is potentially effective in maintaining glycemic control and avoiding of insulin for a mean duration of 7.9 years. Sulfonylurea like glibenclamide and glimepiride are approved by USFDA in combination with metformin [2, 3, 5].

ADVANTAGES OF GLIMEPIRIDE OVER CONVENTIONAL SULFONYLUREA:

- **Binding characteristics:** Glimepiride has a 3 fold higher rate of association from its receptors than glibenclamide. Due to this property glimepiride has a faster action. Glimepiride has a 9 fold higher rate of dissociation from its receptors than glibenclamide. Because of this, glimepiride is associated with a lesser incidence of hyperinsulinemia and hypoglycemia. Least possibility of hyperinsulinemia ensures that glimepiride is a weight neutral sulfonylurea [6-8].

- **Extra pancreatic effects:** Glimepiride has superior extra pancreatic effects than other conventional sulfonylurea as is detected by its blood insulin/blood glucose ratio. A low blood insulin/blood glucose ratio in glimepiride indicates that blood glucose is decreased without abnormal elevations in the plasma insulin levels. Glimepiride due to its additional extra pancreatic effects does not over work the β-cells and has an endogenous insulin sparing action [9].

- **Cardio safety:** The K_{ATP} channels on which the sulfonylurea acts are also present on the myocardium and peripheral blood vessels. Under normal conditions these channels are closed. Only in response to conditions such as hypoxia [decreased oxygen supply] these channels open and decrease the calcium influx resulting in vasodilatation and reduction in the contractility of the heart. This in turn decreases the oxygen requirement. Thus the K_{ATP} channels are part of a cardio protective mechanism known as myocardial preconditioning. The second generation sulfonylurea block the K_{ATP} channels present on the pancreas as well as on the myocardium and peripheral vasculature. It has been documented in vivo studies that glibenclamide prevents myocardial preconditioning. Glimepiride is a sulfonylurea which acts specifically on the K_{ATP} channels on the pancreas to cause insulin release. It does not have any effect on the K_{ATP} channels in the heart and the peripheral vasculature. Thus glimepiride is a cardio safe sulfonylurea and maintains myocardial preconditioning [10].

- **Secondary failure:** Glimepiride by virtue of its extra pancreatic actions improves the utilization of insulin which is released by its pancreatic action. Thus, it does not overwork the β-cells. Hence, the chances of secondary failure with glimepiride are less as compared to glibenclamide [9, 11].

- **Glimepiride is a meal independent sulfonylurea:** While conventional sulfonylurea has to be taken 30 minutes prior to meals, glimepiride can be taken with breakfast or the first main meal of the day [12].

TABLE 1: COMPARISON OF VARIOUS SULFONYLUREAS

SULFONYLUREAS	ONSET (Hours)	HALF LIFE ($T_{1/2}$) (Hours)	DURATION (Hours)	MAXIMUM DOSE (mg/day)
Glipizide	1	3	8-12	40 mg
Glibenclamide	2	6	18-24	20 mg
Gliclazide	1.5	5	12-18	320 mg
Glimepiride	1	9	24	8 mg

TABLE 2: FEATURES AND BENEFITS OF GLIMEPIRIDE

FEATURES	BENEFITS
3 times faster association from receptors	Fast onset of action
9 times faster dissociation from receptors	Least chances of hyper- insulinemia, hypoglycemia, weight gain and secondary failure
No effect on cardiac K_{ATP} channels	Cardio safe, hence safe even in cardiac patients
Weight neutral	Can be used in obese patients
Once daily dosing	Improved patient compliance

CONCLUSION: The alarming spread and rising incidence prompted the formulation of guidelines by a reputed organization like the Indian Council Of Medical Research (ICMR) in collaboration with WHO and ratified by a team of experts in the field. Orally administered antihyperglycemic agents can be used either alone or in combination with other hypoglycemic agent. The current practice of starting therapy with one agent and increasing to maximum dosage before adding a second agent, rather than starting with combination therapy, also needs to be addressed.

There is much evidence to suggest that initiating therapy with lower doses of two agents that have complementary effects can increase the overall efficacy and decreases the incidence of adverse effects. Therefore, combining an insulin-providing agent with an insulin sensitizing agent will augment the efficacy of current antihyperglycemic agents. This is the rational for the development and marketing of sulfonylurea/metformin combination tablets.

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